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Pinto, A.

2018-09

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<http://hdl.handle.net/10138/299788>

<https://doi.org/10.1016/j.ymgmr.2018.07.008>

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A. Pinto^{a,*}, S. Adams^b, K. Ahring^c, H. Allen^d, M.F. Almeida^{e,f,g}, D. Garcia-Arenas^h, N. Arslanⁱ, M. Assoun^j, Y. Atik Altınok^k, D. Barrio-Carreras^l, A. Belanger Quintana^m, S.M. Bernabeiⁿ, C. Bontemps^o, F. Boyle^p, G. Bruni^q, M. Bueno-Delgado^r, G. Caine^s, R. Carvalho^t, A. Chrobot^u, K. Chyż^v, B. Cochrane^w, C. Correia^x, K. Corthouts^y, A. Daly^a, S. De Leo^z, A. Desloovere^{aa}, A. De Meyer^{ab}, A. De Theux^{ac}, B. Didycz^{ad}, M.E. Dijsselhof^{ae}, K. Dokoupil^{af}, J. Drabik^{ag}, C. Dunlop^{ah}, W. Eberle-Pelloth^{ai}, K. Efrting^{aj}, J. Ekengren^{aj}, I. Errekalde^{ak}, S. Evans^a, A. Foucart^{al}, L. Fokkema^{am}, L. François^{an}, M. French^{ao}, E. Forssell^{ap}, C. Gingell^{aq}, C. Gonçalves^{ar}, H. Gökmen Özel^{as}, A. Grimsley^{at}, G. Gugelmo^{au}, E. Gyüre^{av}, C. Heller^{aw}, R. Hensler^{ax}, I. Jardim^{ay}, C. Joost^{az}, M. Jörg-Streller^{ba}, C. Jouault^{bb}, A. Jung^{bc}, M. Kanthe^{bd}, N. Koç^{be}, I.L. Kok^{am}, T. Kozanoğlu^{bf}, B. Kumru^{bg}, F. Lang^{bh}, K. Lang^{bi}, I. Liegeois^{bj}, A. Liguoriⁿ, R. Lilje^{bk}, O. Łubina^{bl}, P. Manta-Vogli^{bm}, D. Mayr^{bn}, C. Meneses^{bo}, C. Newby^{bp}, U. Meyer^{bq}, S. Mexia^{ay}, C. Nicol^b, U. Och^{br}, S.M. Olivas^h, C. Pedrón-Giner^{bs}, R. Pereira^{bt}, K. Plutowska-Hoffmann^{bu}, J. Purves^{ah}, A. Re Dionigi^{bv}, K. Reinson^{bw}, M. Robert^{bx}, L. Robertson^{ah}, J.C. Rocha^{e,g,by,bz}, C. Rohde^{ca}, S. Rosenbaum-Fabian^{cb}, A. Rossi^{cc}, M. Ruiz^{cd}, J. Saligova^{ce}, A. Gutiérrez-Sánchez^h, A. Schlune^{cf}, K. Schulpis^{bm}, J. Serrano-Nieto^{cg}, A. Skarpalezou^{ch}, R. Skeath^{ci}, A. Slabbert^{cj}, K. Straczek^{ck}, M. Giżewska^{ck}, A. Terry^{cl}, R. Thom^{at}, A. Tooke^{aq}, J. Tuokkola^{cm}, E. van Dam^{cn}, T.A.M. van den Hurk^{am}, E.M.C. van der Ploeg^{co}, K. Vande Kerckhove^y, M. Van Driessche^{aa}, A.M.J. van Wegberg^{cp}, K. van Wyk^{cq}, C. Vasconcelos^{cr}, V. Velez García^{cs}, J. Wildgoose^{ct}, T. Winkler^{cu}, J. Żółkowska^v, J. Zuvadelli^{bv}, A. MacDonald^a

^a Birmingham Women's and Children's Hospital, Birmingham, UK

^b Royal Victoria Infirmary, Newcastle, UK

^c Department of PKU, Kennedy Centre, Copenhagen University Hospital, Glostrup, Denmark

^d Sheffield Children's NHS Foundation Trust, UK

^e Centro de Genética Médica, Centro Hospitalar do Porto (CHP), Porto, Portugal

^f Unit for Multidisciplinary Research in Biomedicine, Abel Salazar Institute of Biomedical Sciences, University of Porto-UMIB/ICBAS/UP, Porto, Portugal

^g Centro de Referência na área de Doenças Hereditárias do Metabolismo, Centro Hospitalar do Porto - CHP, Porto, Portugal

^h Congenital and Metabolic Disease Unit, Gastroenterology, Hepatology and Pediatric Nutrition Unit, Sant Joan de Déu Hospital, Barcelona, Spain

ⁱ Dokuz Eylül University Faculty of Medicine, Division of Pediatric Metabolism and Nutrition, Izmir, Turkey

^j Centre de référence des maladies héréditaires du métabolisme, Hôpital Necker enfants Malades, Paris, France

^k Pediatric Metabolism Department, Ege University Medical Faculty, Izmir, Turkey

^l Unidad de Enfermedades Mitocondriales-Metabólicas Hereditarias. Servicio de Pediatría, Hospital 12 de Octubre, Madrid, Spain

^m Unidad de Enfermedades Metabólicas, Servicio de Pediatría, Hospital Ramon y Cajal Madrid, Spain

ⁿ Children's Hospital Bambino Gesù, Division of Artificial Nutrition, Rome, Italy

^o CHRU Clocheville Tours, France

^p National Centre for Inherited Metabolic Disorders, Temple Street Children's University Hospital, Ireland

^q Meyer Children's Hospital, Florence, Italy

^r Children's Hospital Virgen del Rocío, Seville, Spain

^s Mid Yorks NHS Trust, UK

^t Hospital Divino Espírito Santo, Ponta Delgada, Portugal

^u Children Voievodship Hospital, Bydgoszcz, Poland

^v Institute of Mother and Child, Warsaw, Poland

^w Royal Hospital for Children, Glasgow, UK

^x CHLC- Hospital Dona Estefânia, Lisboa, Portugal

^y University hospital Leuven, Belgium

Abbreviations: PKU, Phenylketonuria; Phe, Phenylalanine; IMD, Inherited Metabolic Disorders

* Corresponding author at: Dietetic Department, Birmingham Women's and Children's Hospital, Steelhouse Lane, Birmingham B4 6NH, UK.

E-mail address: alex.pinto@nhs.net (A. Pinto).

<https://doi.org/10.1016/j.ymgmr.2018.07.008>

Available online 08 August 2018

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^z Department of Human Neuroscience, Sapienza University of Rome - Policlinico Umberto I of Rome, Italy

^{aa} University hospital Ghent, Belgium

^{ab} Center of Metabolic Diseases, University Hospital, Antwerp, Belgium

^{ac} IPG (Institut de Pathologie et de Genetique), Charleroi, Belgium

^{ad} University Children's Hospital, Cracow, Poland

^{ae} AMC Amsterdam, Emma Children's Hospital, Netherlands

^{af} Dr. von Hauner Children's Hospital of the University of Munich, Germany

^{ag} University Clinical Center in Gdansk, Poland

^{ah} Royal Hospital for Children Edinburgh, UK

^{ai} Universitäts-Kinderklinik Würzburg, Germany

^{aj} Queen Silvia's Children's Hospital Gothenburg, Sweden

^{ak} Hospital Universitario de Cruces, Vizcaya, Spain

^{al} Cliniques universitaires Saint-Luc, Belgium

^{am} UMC Utrecht, Wilhelmina Children's Hospital, Netherlands

^{an} Hôpital Universitaire Robert-Debré, Centre de référence des maladies héréditaires du métabolisme, Paris, France

^{ao} University Hospitals of Leicester NHS Trust, UK

^{ap} Karolinska University Hospital, Stockholm, Sweden

^{aq} Nottingham Children's Hospital, UK

^{ar} Hospital Central do Funchal, Portugal

^{as} Hacettepe University, İhsan Doğramacı Children's Hospital, Turkey

^{at} Royal Belfast Hospital for Sick Children, Northern Ireland, UK

^{au} Department of Pediatrics, Inherited Metabolic Diseases Unit, University Hospital of Verona, Italy

^{av} Albert Szent-Györgyi Clinical Centre, Hungary

^{aw} Kinder- und Jugendklinik Erlangen, Germany

^{ax} Klinikum Stuttgart Olghospital, Germany

^{ay} Centro Hospitalar Lisboa Norte - H. Sta Maria - Unidade de Doenças Metabólicas, Portugal

^{az} University Children's Hospital, University Medical Center Hamburg Eppendorf, Germany

^{ba} Universitätsklinik Innsbruck department für Kinder- und Jugendheilkunde, Austria

^{bb} CHU Angers, France

^{bc} Charite, Virchow Klinikum Berlin, Germany

^{bd} Skane University Hospital, Sweden

^{be} University of Health Sciences, Ankara Child's Health and Diseases Hematology Oncology Training and Research Hospital, Turkey

^{bf} İstanbul University İstanbul Faculty of Medicine, Turkey

^{bg} Gaziantep Cengiz Gökçek Maternity and Children's Hospital, Turkey

^{bh} University Hospital Mainz, Villa metabolica, Germany

^{bi} Ninewells Hospital, Dundee, UK

^{bj} CHRU Nancy Hospital D'enfants, France

^{bk} Oslo University Hospital, Norway

^{bl} Children's Clinical University Hospital, Riga, Latvia

^{bm} Inborn Errors of Metabolism Department, Institute of Child Health, Athens, Greece

^{bn} Universitätsklinik für Jugend und Kinderheilkunde, Müllner Hauptstr, Salzburg, Austria

^{bo} Hospital de Santo Espírito da Ilha Terceira, EPER, Portugal

^{bp} Bristol Royal Hospital for Children, UK

^{bq} Medical School Hannover, Clinic for Paediatric Kidney- Liver and Metabolic Diseases, Germany

^{br} University Hospital Muenster, Center for Pediatrics, Metabolic Department, Germany

^{bs} Hospital Infantil Universitario Niño Jesús, Madrid, Spain

^{bt} Norfolk & Norwich Hospital, UK

^{bu} The Independent Public Clinical Hospital, No. 6 of the Medical University of Silesia in Katowice John Paul II Upper Silesian Child Health Centre, Poland

^{bv} Department of Pediatrics, San Paolo Hospital, ASST Santi Paolo e Carlo, University of Milan, Italy

^{bw} Tartu University Hospital, Estonia

^{bx} Hôpital Universitaire des Enfants, Reine Fabiola, Bruxelles, Belgium

^{by} Faculdade de Ciências da Saúde, Universidade Fernando Pessoa, Portugal

^{bz} Centre for Health Technology and Services Research (CINTESIS), Portugal

^{ca} Hospital for Children and Adolescents, Department of Women and Child Health, University Hospitals, University of Leipzig, Germany

^{cb} Department of General Pediatrics, Adolescent Medicine and Neonatology, Medical Center – University of Freiburg, Faculty of Medicine, Freiburg, Germany

^{cc} Division of Inherited Metabolic Diseases, Reference Centre Expanded Newborn Screening, Department of Woman's and Child's Health, University Hospital of Padua, Italy

^{cd} Hospital Universitario Nuestra Señora de Candelaria, Tenerife, Spain

^{ce} Children's Faculty Hospital, Kosice, Slovakia

^{cf} Department of General Pediatrics, Neonatology and Pediatric Cardiology, University Children's Hospital Duesseldorf, Heinrich Heine University, Düsseldorf, Germany

^{cg} HRU Málaga, Spain

^{ch} Institute of Child Health, "A. Sophia" Children's Hospital, Athens, Greece

^{ci} Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

^{cj} Evelina Children's Hospital, Guy's & St. Thomas' NHS Foundation Trust, London, UK

^{ck} Clinic of Pediatrics, Endocrinology, Diabetology, Metabolic Diseases and Cardiology of the Developmental Age Pomeranian Medica University, Poland

^{cl} Alder Hey Children's NHS Foundation Trust, Liverpool, UK

^{cm} Clinical Nutrition Unit, Internal Medicine and Rehabilitation and Pediatric Hospital, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

^{cn} University of Groningen, University Medical Center Groningen, Beatrix Children's Hospital, Department of Dietetics, Groningen, Netherlands.

^{co} Maastricht University Medical Centre, Maastricht, Netherlands

^{cp} Department of Gastroenterology and Hepatology - Dietetics, Radboud University Medical Centre, Nijmegen, Netherlands

^{cq} Manchester University NHS Foundation Trust, UK

^{cr} Centro Hospitalar São João, Porto, Portugal

^{cs} Unit of Nutrition and Metabolopathies, Hospital La Fe, Valencia, Spain

^{ct} Bradford Teaching Hospitals St Lukes, UK

^{cu} Klinik für Kinder- und Jugendmedizin, Carl-Thiem-Klinikum gGmbH Cottbus, Germany

ARTICLE INFO

Keywords:

Breastfeeding
Infant practices
Phenylketonuria
Phenylalanine
Phe-free infant formula

ABSTRACT

Background: In infants with phenylketonuria (PKU), dietary management is based on lowering and titrating phenylalanine (Phe) intake from breast milk or standard infant formula in combination with a Phe-free infant formula in order to maintain blood Phe levels within target range. Professionals use different methods to feed infants with PKU and our survey aimed to document practices across Europe.

Methods: We sent a cross sectional, survey monkey® questionnaire to European health professionals working in IMD. It contained 31 open and multiple-choice questions. The results were analysed according to different geographical regions.

Results: Ninety-five centres from 21 countries responded. Over 60% of centres commenced diet in infants by age 10 days, with 58% of centres implementing newborn screening by day 3 post birth. At diagnosis, infant hospital admission occurred in 61% of metabolic centres, mainly in Eastern, Western and Southern Europe. Breastfeeding fell sharply following diagnosis with only 30% of women still breast feeding at 6 months.

53% of centres gave pre-measured Phe-free infant formula before each breast feed and 23% alternated breast feeds with Phe-free infant formula. With standard infant formula feeds, measured amounts were followed by Phe-free infant formula to satiety in 37% of centres ($n = 35/95$), whereas 44% ($n = 42/95$) advised mixing both formulas together. Weaning commenced between 17 and 26 weeks in 85% centres, ≥ 26 weeks in 12% and < 17 weeks in 3%.

Discussion: This is the largest European survey completed on PKU infant feeding practices. It is evident that practices varied widely across Europe, and the practicalities of infant feeding in PKU received little focus in the PKU European Guidelines (2017). There are few reports comparing different feeding techniques with blood Phe control, Phe fluctuations and growth. Controlled prospective studies are necessary to assess how different infant feeding practices may influence longer term feeding development.

1. Background

Infants with phenylketonuria (PKU) with blood Phe $> 360 \mu\text{mol/L}$ are treated with a low phenylalanine (Phe) diet following diagnosis after a positive newborn screening test. This involves restricting natural protein intake by lowering the amount of breast milk or standard infant formula given in combination with a protein substitute (Phe-free infant formula). The practical feeding process can be conducted in different ways and it is likely that practices may vary throughout Europe. Although it is well established that commencing treatment early is associated with better outcome in PKU, it is possible that the choice and application of infant feeding practices may also affect longer-term feeding development and nutritional outcome. In the general population, breastfeeding is associated with less overweight and obesity and a higher IQ [1]. Also a higher protein intake in infancy may be associated with a later risk of obesity [2]. Approaches to the delivery of early care, support and education in PKU may affect parental acceptance of the condition and their attitude towards dietary management. On diagnosis of PKU, parents are expected to manage the dietary treatment immediately, and so are forced into a situation of coping (what must be done here and now) rather than being given time to adjust to the diagnosis of PKU in their infant [3]. Feeding infants with PKU is undoubtedly challenging. The goal of nutritional management is to maintain blood Phe levels between 120 and $360 \mu\text{mol/L}$ as recommended by the PKU European guidelines [4]. Timing of treatment commencement is determined by the age of newborn screening. If the age of newborn screening is later, in infants with classical PKU it is probable that blood Phe concentrations will be higher, and in turn it will take longer to stabilise blood Phe control, although this remains unreported in screened infants. Later newborn screening will require rapid reduction of blood Phe, possibly leading to temporary cessation of breastfeeding and overall, this may cause additional parental anxiety associated with feeding. Also, in slightly later diagnosed infants, well-established feeding routines pre-diagnosis may be more challenging to change, and the introduction of a strong tasting Phe-free infant amino acid formula (providing non Phe amino acids with other essential nutrients) may be difficult. The European guidelines recommend that treatment should commence by 10 days of age, however it is unknown how many European centres are able to achieve this target [4].

Dietary management in infancy is based on lowering and titrating dietary Phe intake from breast milk or standard infant formula so that

blood Phe concentrations are maintained within target range whilst achieving optimal growth and development. There appears no universal approach to feeding infants with PKU, with health professionals adopting many different practices. For example, when partial breast milk is given, techniques may include: 1) a measured amount of expressed breast milk prior to a Phe-free infant formula [5], 2) a pre-measured amount of Phe-free infant formula prior to breastfeeding until satiety [6–8], 3) a pre-measured amount of Phe-free infant formula prior to ‘time-controlled’ breastfeeding, and 4) alternate breast and Phe-free infant formula feeds [9–11]. When a measured amount of standard infant formula is given, this may be administered pre or post Phe-free infant formula or both feeds may be mixed together [10, 12]. In addition, whilst it is known that breastfeeding management strategies vary among countries and between treatment centres within countries [7, 13–16], it is unknown if the type of strategy will impact on the duration of breastfeeding in PKU.

In our survey, we aimed to study dietary treatment methods in infants with PKU across European centres.

2. Material and methods

A cross sectional, survey monkey® questionnaire was sent to European IMD health professionals (dietitians, nutritionists and medical doctors) who were either members of the ‘The Society for the Study of Inborn Errors of Metabolism’ (SSIEM) or who have participated in previous European surveys assessing dietary practices [17–19]. The questionnaire was composed of 31 open and multiple-choice questions asking questions about the infant age at newborn screening and dietary feeding practices at diagnosis and during the first 12 months of life. The questionnaire was written in English but linguistic support (Portuguese, French, Spanish and Italian) was provided by the first author [AP] to clarify any queries. Only one answer per centre was accepted from health professionals and participants were instructed to answer each question according to their general clinical practice rather than with individual patient cases.

The questionnaire responses were analysed by individual centre in addition to the geographical region of each centre. The results were analysed in two parts 1) processes related to early feeding and 2) weaning processes (introduction of low protein foods, normal foods and change in protein substitutes).

In part 1, the following information was collected: number of infants

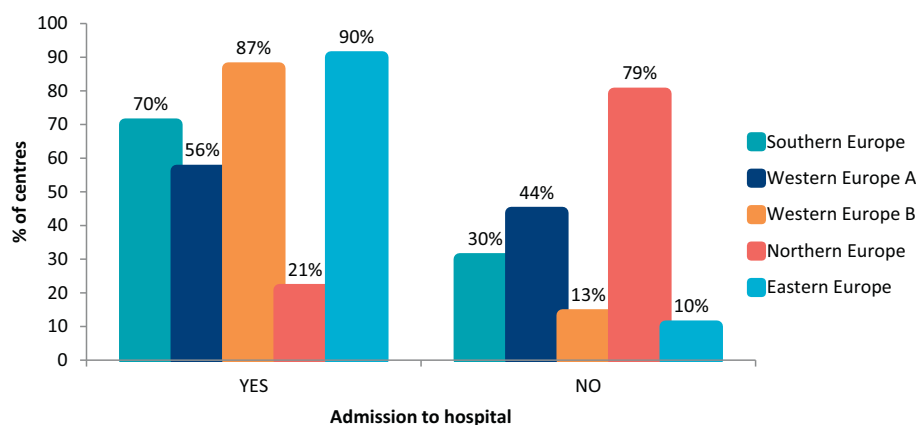


Fig. 1. Percentage of centres who admitted infants to hospital on diagnosis of PKU.

diagnosed with PKU each year, infant age at newborn-screening, age of starting diet, hospital or home care at diagnosis, frequency of blood Phe monitoring, breastfeeding prevalence at diagnosis and post diagnosis, and duration of breastfeeding. Breastfeeding was defined as the only source of feed intake before diagnosis. Post diagnosis of PKU breastfeeding was defined as breast milk given with Phe-free infant formula.

Detail about the different methods of administering Phe-free infant formula with breast milk or standard infant formula was collected. Data on total protein requirements was also collected. Part 2 results will be published separately.

3. Results

3.1. Participants

Ninety-five centres from 21 European countries responded to the survey monkey® questionnaire. Centres were grouped into the following geographical regions to analyse the results:

- Southern Europe ($n = 30$ centres): Portugal ($n = 7$ centres), Italy ($n = 6$ centres), Spain ($n = 9$ centres), Greece ($n = 2$ centres) and Turkey (6 centres);
- Western Europe A ($n = 16$ centres): Belgium ($n = 6$ centres), France ($n = 5$ centres) and The Netherlands ($n = 5$ centres);
- Western Europe B ($n = 15$ centres): Germany ($n = 13$ centres) and Austria ($n = 2$ centres);
- Northern Europe ($n = 24$ centres): UK ($n = 17$ centres), Sweden ($n = 3$ centres), Norway ($n = 1$ centre), Denmark ($n = 1$ centre), Finland ($n = 1$ centre) and Ireland ($n = 1$ centre);

- Eastern Europe ($n = 10$ centres): Latvia ($n = 1$ centre), Poland ($n = 6$ centres), Slovakia ($n = 1$ centre), Hungary ($n = 1$ centre) and Estonia ($n = 1$ centre).

The number of new infants diagnosed with PKU annually in each centre varied widely but over half of the respondents only had 1 to 3 new cases per year. The number of new infants diagnosed per year in centres were: 1–3 cases per annum, 52% ($n = 49/95$); 4–10 cases, 31% ($n = 29/95$); 11–20 cases, 11% ($n = 10/95$); 21–30 cases, 1% ($n = 1/95$); and ≥ 30 cases, 2% ($n = 2/95$).

New born screening occurred by day 3 of infant age in over 50% of centres: day 1, 2%, ($n = 2/95$) centres; day 2, 24%, ($n = 23/95$); day 3, 32% ($n = 30/95$); day 4–6 days, 38% ($n = 36/95$); day 7–10, 3% ($n = 3/95$); and > 10 day, 1% ($n = 1/95$) centres.

3.2. Dietary practices after diagnosis

At diagnosis, infants were admitted to hospital in 61% of metabolic centres ($n = 58/95$ centres). The centres more likely to admit patients to hospital at the time of diagnosis were in Eastern Europe, Western Europe and Southern Europe (Fig. 1). Over 60% of centres (Southern Europe: 53%; Western Europe A: 69%; Western Europe B: 93%; Northern Europe: 63%; Eastern Europe: 30%) had commenced a low Phe diet by 10 days of age (< 3 days, 1% [$n = 1/95$]; 4–10 days, 61% [$n = 58/95$]; 11–14 days, 31% [$n = 29/95$]; 15–20 day, 6% [$n = 6/95$]; > 21 days, 1% [$n = 1/95$] of centres). Only 42% of centres were likely to have 76% or more of their infants on breast feeds at the time of diagnosis, with breastfeeding being highest in Southern and Western Europe (Fig. 2, Table 1). The numbers of infants who continued

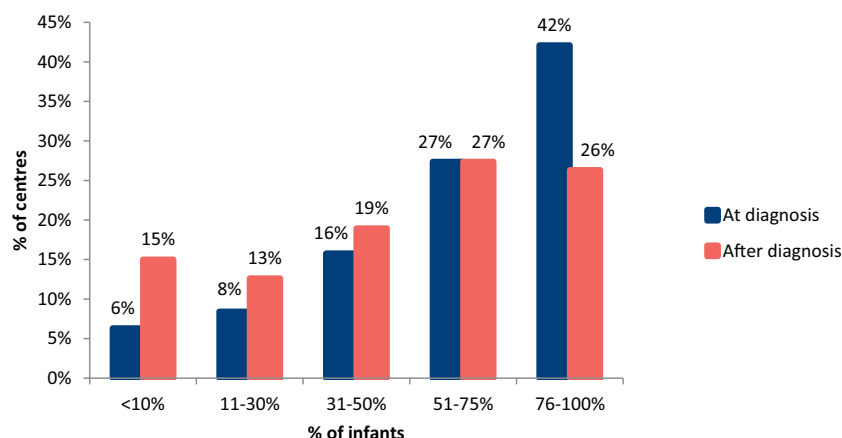


Fig. 2. Percentage of centres breastfeeding infants with PKU at time of diagnosis and post diagnosis.

Table 1

Infants that were breast fed at the time of PKU diagnosis in the different European geographical regions.

Geographical region	% of centres with specific % of infants with PKU that were breast-fed AT TIME OF DIAGNOSIS				
	< 10%	11–30%	31–50%	51–75%	76–100%
Southern Europe N = 30	10% (3/30)	7% (2/30)	7% (2/30)	16% (5/30)	60% (18/30)
Western Europe A N = 16	0	13% (2/16)	19% (3/16)	44% (7/16)	25% (4/16)
Western Europe B N = 15	0	0	0	47% (7/15)	53% (8/15)
Northern Europe N = 24	12% (3/24)	12% (3/24)	38% (9/24)	12% (3/24)	26% (6/24)
Eastern Europe N = 10	0	10% (1/10)	10% (1/10)	40% (4/10)	40% (4/10)

breastfeeding fell markedly and only 26% of centres maintained 76% or more of their infants on breast feeds beyond the diagnostic time (Fig. 2, Table 2). Overall, breastfeeding duration was short with a mean of: 4 weeks in 9% ($n = 9/95$), 5–17 weeks in 26% ($n = 25/95$), 18–26 weeks in 34% ($n = 32/95$), 27–52 weeks in 24% ($n = 23/95$) and > 1y, 6% ($n = 6/95$) of centres. Different geographical results are presented in Table 3. Only 17% of centres ($n = 16/95$) pre-measured expressed breast milk.

In breastfeeding infants, 53% ($n = 50/95$ centres) of centres gave a measured amount of Phe-free infant formula before each breast feed to satiety (without any time limited breast feeds); 11% ($n = 10/95$) gave a pre-measured amount of Phe-free infant formula before time limited breast feeds and 6% ($n = 6/95$) gave breast feeds followed by a measured amount of Phe-free infant formula from a bottle. Twenty-three per cent ($n = 22/95$ centres) gave alternate breast feeds with phe-free infant formula and 7% ($n = 7/95$ centres) used different practices.

When a standard infant formula feed was given for the Phe source, 8% ($n = 8/95$ centres) of centres gave a measured amount of Phe-free infant formula first followed by measured amount of standard infant formula, whereas 37% ($n = 35/95$) gave a measured amount of standard infant formula followed by Phe-free infant formula to satiety. Forty-four per cent of centres ($n = 42/95$) advised mixing Phe-free formula together with standard infant formula, 8% ($n = 8/95$ centres) alternated feeds of standard infant formula with Phe-free infant formula and 2% ($n = 2/95$ centres) used different practices. Fig. 3 indicates the different practices by geographical regions.

The total protein requirements (including both natural protein and protein equivalent from protein substitute) prescribed by centres in the first 12 months of life were: 1.5 g/kg/day, 1% ($n = 1/95$); 2 g/kg/day, 24% ($n = 23/95$); 2.5 g/kg/day, 36% ($n = 34/95$); 3 g/kg/day, 36% ($n = 34/95$ centres); 3.5 g/kg/day, 1% ($n = 1/95$ centres) and undefined 2% ($n = 2/95$ centres). Table 4 presents the amounts

Table 2

Infants that were breast fed post PKU diagnosis in the different European geographical regions.

Geographical region	% of centres with specific % of infants with PKU that CONTINUE to breastfeed AFTER diagnosis				
	< 10%	11–30%	31–50%	51–75%	76–100%
Southern Europe N = 30	23% (7/30)	10% (3/30)	10% (3/30)	20% (6/30)	37% (11/30)
Western Europe A N = 16	13% (2/16)	19% (3/16)	25% (4/16)	13% (2/16)	31% (5/16)
Western Europe B N = 15	0	0	13% (2/15)	67% (10/15)	20% (3/15)
Northern Europe N = 24	17% (4/24)	17% (4/24)	29% (7/24)	17% (4/24)	20% (5/24)
Eastern Europe N = 10	10% (1/10)	20% (2/10)	20% (2/10)	40% (4/10)	10% (1/10)

Table 3

Duration of infant breastfeeding by European geographical region (%).

Geographical region	Duration of breastfeeding				
	4 weeks	5–17 weeks	18–26 weeks	27–52 weeks	> 1y
Southern Europe N = 30	23% (7/30)	27% (8/30)	23% (7/30)	10% (3/30)	17% (5/30)
Western Europe A N = 16	6% (1/16)	50% (8/16)	25% (4/16)	19% (3/16)	0
Western Europe B N = 15	0	13% (2/15)	47% (7/15)	40% (6/15)	0
Northern Europe N = 24	4% (1/24)	21% (5/24)	42% (10/24)	33% (8/24)	0
Eastern Europe N = 10	0	20% (2/10)	40% (4/10)	30% (3/10)	10% (1/10)

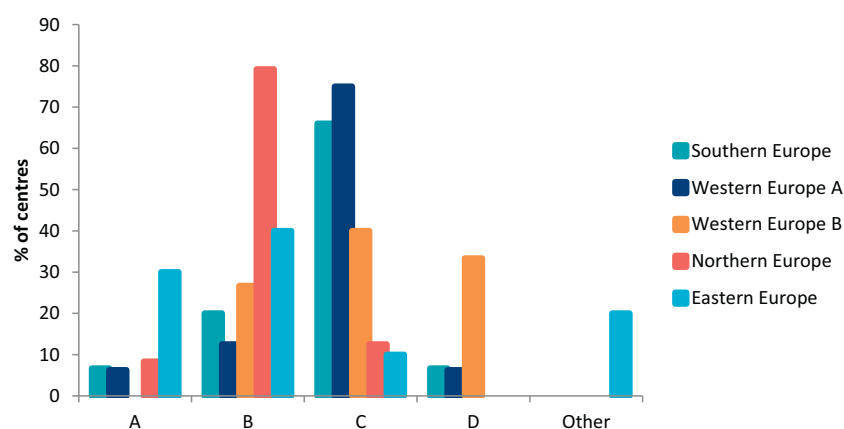


Fig. 3. Description by different European geographical regions of how Phe-free infant formula is given when a standard formula is used to provide the phenylalanine source. Abbreviations: A: give a measured amount of Phe-free infant formula first followed by a measured amount of standard infant formula; B: give a measured amount of standard infant formula followed by Phe-free infant formula to satiety; C: mix Phe-free infant formula with standard infant formula; D: alternate feeds of standard infant formula and Phe-free Infant formula.

Table 4

Total protein prescribed (g/kg/day) to infants with PKU by different European geographical regions (%).

Geographical region	Total protein prescription					
	1.5 g/kg/day	2.0 g/kg/day	2.5 g/kg/day	3.0 g/kg/day	3.5 g/kg/day	other
Southern Europe N = 30	3% (1/30)	13% (4/30)	43% (13/30)	37% (11/30)	4% (1/30)	0
Western Europe A N = 16	0	38% (6/16)	56% (9/16)	6% (1/16)	0	0
Western Europe B N = 15	0	73% (11/15)	20% (3/15)	0	0	7% (1/15)
Northern Europe N = 24	0	4% (1/24)	21% (5/24)	75% (17/24)	0	4% (1/24)
Eastern Europe N = 10	0	10% (1/10)	40% (4/10)	50% (5/10)	0	0

prescribed by different geographical regions.

The majority of centres (85% [$n = 81/95$]) started weaning with phe-free solids between 17 and 26 weeks, 3% of centres ($n = 3/95$) before 17 weeks and 12% ($n = 11/95$) after 26 weeks of age.

During the first year of life following blood Phe stabilization, blood Phe levels were monitored by centres: twice weekly by 16% ($n = 15/95$); weekly by 69% ($n = 66/95$); once every 2 weeks by 11% ($n = 10/95$) and monthly by 4% ($n = 4/95$) of centres.

4. Discussion

This is the largest survey conducted on infant feeding practices in PKU throughout Europe. Methods used to feed infants with PKU varied widely across centres. Our study indicated that over 60% of centres had started dietary treatment by the time infants were 10 days of age. It is encouraging that many centres met the European PKU guidelines [4]. Earlier newborn screening prevents severe neurological impairment as well as permitting timely implementation of the Phe restricted diet, although it is unclear how this impacts on long term feeding.

The need to admit infants into hospital at the time of diagnosis is associated with availability of local resources, traditional local practices or early testing for BH4 responsiveness. It is unknown if hospital admission is associated with earlier stabilization of blood Phe levels, alleviation or heightening of parental anxiety.

Although the use of breastfeeding in PKU is well established, the percentage of centres breastfeeding was highly variable between regions: Southern, Western (Germany and Austria) and Eastern Europe had the highest incidence of breastfeeding at the time of diagnosis, but the numbers fell in both Eastern and Western European countries following diagnosis. Some countries in Northern Europe (mainly UK) had

a lower rate of breastfeeding at diagnosis but infants were a little older at diagnosis with a mean diagnostic age of > 10 day.

In PKU, breastfeeding maintenance is more complex than in the general population. The availability of home support with reliable and consistent advice is important, but at diagnosis mothers have to make immediate decisions about feeding choice. Blood Phe levels above 1000 $\mu\text{mol/L}$ at diagnosis may require cessation of breastfeeding for 24 to 48 h, and any difficulty in re-establishing breast feeds, may lead to breastfeeding failure. Mothers are commonly overwhelmed and distressed; they are uncertain and anxious about the amount of breast milk consumed and the potential harm this may cause to the baby.

With breastfeeding, the most common practice was to administer a pre-measured amount of Phe-free formula prior to breast-feeds. Surprisingly, alternating feeds of breast milk and Phe-free infant formula was practiced in 23% of centres. There are few reports describing the use of this method [6, 10, 11]. It will probably work well in early infancy when Phe requirements are high, but as this decreases with age, it may be necessary to further limit the number of daily breast feeds offered and replace this with additional Phe-free formula. This may lead to uneven distribution of Phe intake causing increased fluctuation in blood Phe concentrations. Prospective, controlled studies examining this technique are required to study 24 h blood Phe variation but the simplicity of this technique is very attractive.

Some centres ask mothers to only express breast milk so that it can be pre-measured, but there are now many longitudinal retrospective studies on large numbers of infants that show that giving pre-measured Phe-free infant formula before breastfeeding to satiety is safe and satisfactory blood Phe control and growth is achievable [8, 20, 21].

Only 30% of breastfeeding women continued to breast feed beyond 6 months. This was highly variable from 19% centres in Western Europe

A to 40% in Western Europe B and Eastern Europe. Overall this data confirms previous findings, which clearly and consistently indicate that breastfeeding is commonly for a short duration in PKU [8, 10, 11, 14, 15, 22–25]. Interestingly, even though Northern Europe is the region with a lower percentage of breastfeeding infants at diagnosis, their percentage of continuation is similar to other regions (33%) and by 6 months of age, breastfeeding rates (34%) were close to the normal population [26].

For infants who were given standard infant formula the most popular method was mixing standard infant formula together with Phe-free infant formula, although this technique is under researched [11, 12]. It is certainly more convenient for parents but when Phe sources are introduced from food, a lower volume of standard infant formula is mixed with the Phe-free infant protein substitute leading to a stronger taste of the latter and possibly lower acceptance by the infant. There are few longitudinal studies examining different methods of bottle feeding in PKU and the impact on blood Phe control as well as later adherence to protein substitute.

The amount of total protein prescribed (97% prescribed ≥ 2 g/kg/day) was higher than the European guidelines (2017) [4]. In the European guidelines, it is recommended an additional 40% more protein from Phe-free amino acids is given compared with the WHO/FAO/UNU 2007 safe levels of protein intake [27], but this figure is empirically based. There have been reports of poor growth in young children with PKU [4], and Hoeksma demonstrated that a higher intake of natural protein intake, rather than the total protein intake was an important factor in head circumference growth [28]. There are also reports to indicate that higher doses of protein substitute improve natural protein tolerance in young children [4]. We consider further evidence is required before centres reduce doses of protein substitute in infancy according to the new European guidelines (2017) [4].

This study has several limitations. It was cross-sectional rather than prospective. Data about blood Phe control measurements were not collected. Data was collected about general practice rather than individual prescriptions. Only one questionnaire was completed by each PKU centre and it was possible that different professionals may have had different practices within the same centre. Moreover, different access to special formula, experience of professionals and ability to do home blood sampling may have influenced practices.

5. Conclusion

Even though PKU is the most commonly studied inherited metabolic disorder, infant feeding practices varied widely across Europe. Interestingly, little attention was paid to this subject in the PKU European Guidelines (2017) [4] and there are few reports comparing different feeding techniques with blood Phe control, stability of blood Phe levels and growth. Controlled prospective studies are needed to assess how different practices influence these outcomes in order to define the optimal infant feeding practices in PKU.

Author's contributions

AP and AM developed the questionnaire, interpreted data, analysed data and wrote the first draft of the manuscript. All the remaining authors were involved in data collection, interpretation of data and critical revision of the paper for important intellectual content and final approval of the version before publication.

Funding

Funding was not needed to develop this study.

Availability of data and materials

The datasets used and/or analysed during this current study are

available from the corresponding author upon request.

Ethics approval and consent to participate

This was not applicable as this survey collected information about health professional's practice rather than individual patient data.

Consent for publication

Health professionals were made aware that the results of the survey would be published and gave their consent when participating.

Competing interests

Alex Pinto has received an educational grant from Cambrooke Therapeutics and grants from Vitaflo, Nutricia, Merck Serono and Biomarin to attend scientific meetings. Anne Daly has undertaken evaluation work for the nutritional companies – Vitaflo Ltd., Nutricia Ltd. and Metax. Sharon Evans is a research dietitian funded by Nutricia; financial support from Nutricia and Vitaflo to attend study days and conferences. Júlio César Rocha is member of the European Nutrition Expert Panel (Biomarin) and member of an Advisory Board for Applied Pharma Research. Anita MacDonald has received research funding and honoraria from Nutricia, Vitaflo International and Merck Serono. She is a member of the European Nutrition Expert Panel (Biomarin), member of Sapropterin Advisory Board (Biomarin), member of the Advisory Board entitled ELEMENT (Danone-Nutricia), and member of an Advisory Board for Arla and Applied Pharma Research. Rita Carvalho received grants to attend scientific meetings from Biomarin and Jaba Recordati. Liesbeth van der Ploeg received grants from Nutricia and from Vitaflo to attend scientific meetings on the field of metabolic diseases. Agnieszka Chrobot declares grants to attend scientific meetings from Nutricia, Vitaflo and Mead Johnson. Kamilla Straczek received honoraria from Nutricia Metabolics, Vitaflo and Mead-Johnson. Maria Gżewska received honoraria and was a consultant for: Nutricia International/Danone, Merck-Serono, Mead Johnson, BioMarin and Vitaflo. Alice Rossi has received funding from Biomarin, Nutricia, Piam Farmaceutici and Vitaflo to attend scientific meetings and courses. She is also a member of the European Nutritionist Expert Panel in PKU (Biomarin). Katharina Dokoupil has received honoraria from Nutricia, Vitaflo, Merck Serono and Dr. Schär and is a member of the European Nutrition Expert Panel (Biomarin), member of a Nutricia Advisory Board and member of a Nestlé Advisory Board. Consuelo Pedrón-Giner has received support from Vitaflo to attend SSIEM meetings. Ulrike Och declares grants to attend scientific meetings from Biomarin and Dr. Schär. Barbara Cochrane has received research funding and honoraria from Nutricia and Vitaflo International. The remaining authors declare no competing interests.

Acknowledgments

We thank Vitaflo for supporting the publication cost of this paper.

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